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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	

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34

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/386,709	Brayden
Examiner	**Art Unit**
Jennifer Graser	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *RCE & Amendt. D, 8/22/03*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-9, 11, 12, 21-25, 27-31, 33, 35, 38, 39, 41, and 42* is/are pending in the application.

4a) Of the above, claim(s) *1-3, 5-9, 11, and 12* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-25, 27-31, 33, 35, 38, 39, 41, and 42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on */31/99 (see O.actior* is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32&33*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/22/03, Amendment D, has been entered.

Claims 21-25, 27-31, 33, 35 and 38, 39, 41 and 42 are currently under examination.

Drawings

2. The Application was filed with only 6 drawings. However, the 'Brief Description of Drawings' and the Examples in the Specification refer to a 'Figure 7'. Page 24 refers to Figure 7 yet no Figure 7 was filed. No Figure 7 has ever been received. Appropriate correction is requested.

Information Disclosure Statement

3. Applicants have submitted over one hundred references to be considered by the Examiner. Many of these references are one hundred pages long. No summary of the references was provided. Given the examination time constraints per application coupled with the fact that several hundred more references were reviewed from the Examiner's own literature search, the references listed on the PTO-1449 were given an initial cursory review with only the references which seemed to be most pertinent receiving a more thorough review. Applicant is encouraged

to point out the most relevant references related to the claimed invention for more intense review in case some of the most pertinent passages were buried amongst the less relevant art and inadvertently missed by the Examiner.

Specification

4 The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Original claims 6 and 12 recite vaccine formulations for oral administration which comprise at least two subpopulations of microparticles [nanoparticles], each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer. Since the claims provide mention of oral administration, they are deemed sufficient to provide support for methods of *inducing a protective immune response, said method comprising orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation*. However, the terminology " at least two subpopulations of microparticles [nanoparticles], each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer" cannot be found in the body of

the specification. Applicants should amend the specification to provide proper antecedent basis for the claimed subject matter.

Claim Rejections - 35 USC § 112-Enablement

5. Claims 21-25, 27-31, 33, 35, 38, 39, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabled for 'methods of inducing a protective immune response wherein said method comprises orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation...". The specification fails to provide any description of such a method, nor are any results provided for such a method. The specification has demonstrated with challenge results that a single antigen encapsulated in a microparticle and administered orally provides protection against the wild-type organism and have also demonstrated that two antigens encoded together within the same microcapsule and orally administered can also provide protection. However, the specification is silent on the oral administration of two subpopulations of microparticles each containing a different antigen. The prior art teaches that the vaccine art is

highly unpredictable. It has also taught that multivalent vaccines are unpredictable and often times less effective than a single antigen vaccine in providing protection due to antigenic competition between the two antigens. Applicants stated in the Amendment filed February 26, 2002 on page 6 that support and enablement for this method could be found in Examples 7 and 8. However, a recent review of Examples 7 and 8 does not describe "a first and second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation". Example 7 teaches microparticles with Ptd and FHA together in a single microparticle, not each in their own microparticle as required by the claim. The Example refers to 4 different test groups in which the first group received control PLG (empty PLG microparticles), the second group received Ptd entrapped in PLGA micropartcles, the third group received Ptd SOLUTION and the fourth group received microparticles containing both Ptd and FHA entrapped in the same microparticles (i.e., 100ug of each antigen not two different subpopulations of microparticles). Results for the microparticles containing both antigens are provided. Figure 6 further demonstrates the results which do not include an experiment in which a first and second subpopulation of microparticles, each containing a different antigen are administered to a mouse.

Example 8 also fails to provide enablement for this limitation. Example 8 describes three different groups of mice. The first group received Ptd and FHA in saline. The second group

received Ptd and FHA together in the same microparticles. The third group received empty nanoparticles. No results of immunization experiments which administered two subpopulations containing different antigens are provided, nor does the specification mention any such experiments. The entire body of the example refers to Ptd and FHA together in solution or Ptd and FHA entrapped in PLGA. There is no mention of two different subpopulations of microparticles, each containing a different antigen.

Page 5, lines 28-29, recites that "[p]referably, the microparticles or nanoparticles contain at least two *B.pertussis* antigens, such as inactivated *B.pertussis* toxin or FHA". No mention is made of two subpopulations of microparticles each containing a different antigen. Which further supports that the Ptd and FHA antigens used in Examples 7 and 8 were entrapped in the same microparticles. No mention is made of the antigens being separately encapsulated and in two different populations.

Further, as pointed out by Applicants in their response of July 30, 2003, Shahin et al teach that administration of microencapsulated FHA fails to stimulate a protective mucosal response via the oral route yet were successful with the intranasal administration of microencapsulated FHA. Jones et al indicate success with oral administration of a single population of microencapsulated fimbriae antigen. Since Shahin et al were unable to produce an adequate immune response after oral immunization with microencapsulated FHA, the same vaccine which is being used in the invention, it is unclear that methods which use microparticles containing FHA as recited in claims 25, 31 and 33, and would work as oral vaccines. It is even

more unpredictable that two subpopulations of microencapsules containing different antigens would provide success. Given the unpredictability in the prior art coupled with the claims requirement for 'protection' results from challenge experiments using the methods as instantly claimed are required to support enablement. The instant specification fails to describe the instantly claimed methods and further fails to provide any results from experiments which use a first and second subpopulation of microparticles each containing a different antigen and co-administered orally.

Applicants have referred to results that show that PT+FHA gives better than 2 Log10 units improvement over PT alone; however, these results are not commensurate in scope with the claimed invention because the PT and FHA were encapsulated in the same microcapsule and not in separate microcapsules as required by the claim. As the prior art has demonstrated, this difference is significant and appears to be what Applicants deem distinguishing over the prior art.

The specification is also not enabled for methods which use *any* antigens in the immunization methods. The specification has only demonstrated results with the single encapsulation of a FHA or Ptd or the two antigens encapsulated together. The specification provides no results for the scope of the current claims; i.e., methods of inducing a protective immune response wherein said method comprises orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the

micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation', nor does it provide results for any multivalent vaccines with antigens other than the pertussis antigens. Additional evidences may be provided to enable the scope of the invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 21-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt et al (US 5,897,867) in further view of Singh et al (Vaccine, 1998, 16(4): 346-352) and Shahin et al. (Infect.Immun., Apr.1995, 63(4): 1195-1200).

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could *protect* mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, i.e., less than 3um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). The microparticles were prepared through a solvent extraction technique (top of page 490, column 1). It is further disclosed that analysis of

the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). It is further disclosed that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1).

However, Jones et al does not particularly exemplify the use of at least a first and second subpopulation of microparticles wherein each subpopulation comprises different antigens.

Eckhardt et al teach a multivalent vaccine against *Bordetella pertussis* comprising a combination of individually purified pertussis antigens. Eckhardt teach that other antigens, besides just FHA or LPF and FHA, are needed to obtain efficacious pertussis vaccines. See paragraph bridging columns 1 and 2.

Singh et al teaches the entrapment of two different antigens in the same microparticle. See page 347, second paragraph in column two. Singh teaches that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens int he same microparticles because of the possibility that the presence of two antigens within the same microparticles results in poorer antigen presentation. These teachings do not suggest that two different antigens encapsulated in two different microparticles would suffer from this same antigenic competition. Singh et al disclose that diphtheria toxoid was encapsulated in microparticles prepared from polylactide-co-glycolide (PLG) polymers using a solvent evaporation technique (abstract). It is disclosed that rats were immunized with PLG

microparticles containing the diphtheria toxoid with all microparticles being less than 10um. Another group of mice were given microparticles of greater than 10um. See page 348, column 1. It is disclosed that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 2).

Shahin et al discloses that microencapsulated pertussis toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally (abstract). It is also disclosed that intranasal administration of these microencapsulated antigens elicited high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract, i.e., a TH2-polarized protective immune response (abstract). Shanin specifically discloses that intranasal administration of a combination of 1ug each of *each* of the microencapsulated B.pertussis antigens (i.e, microencapsulated pertussis toxoid; microencapsulated filamentous hemagglutinin; and microencapsulated pertactin) was more effective in reducing bacterial infection than administration of any single microencapsulated antigen. See abstract. This teaches that subpopulations of different microencapsulated antigens from *B.pertussis* allow for a better immune response than a single microencapsulated population intranasally. Although Shahin teaches that success was not found with oral administration of single population of microencapsulated FHA antigen, the reference teaches this is most likely due to the amount of microcapsules administered orally since it was well known in the prior art that less than 1% or an oral dose of DL-PLG microspheres successfully reaches the Peyer's patches. It is noted that Shahin et al did not attempt to increase

the dose of microcapsules orally administered, nor did Shahin try orally administering three subpopulations of all three pertussis antigens as was done intranasally.

It would have been prima facie obvious to one of ordinary skill in the art to include an additional *B.pertussis* antigen in the oral administration methods taught by Jones et al. because Eckhardt teaches that multivalent vaccines are needed to obtain efficacious pertussis vaccines. One of ordinary skill in the art would also have been motivated to encapsulate this antigen as was done with the pertussis antigen in the method taught by Jones because Jones teaches that the oral administration of a microencapsulated antigen can confer protection at a remote mucosal surface and the microencapsulation prevents the antigen from getting broken down in the gut which is a significant advantage over other routes of administration. One of ordinary skill in the art would have been further motivated to individually encapsulate the antigens instead of combining them together in a single microcapsule because Singh teaches that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens int he same microparticles because of the possibility that the presence of two antigens within the same microparticles results in poorer antigen presentation. Further, Shahin teaches that the intranasal administration of a combination of 1ug each of *each* of the microencapsulated B.pertussis antigens (i.e, microencapsulated pertussis toxoid; microencapsulated filamentous hemagglutinin; and microencapsulated pertactin) was more effective in reducing bacterial infection than intranasal administration of any single microencapsulated antigen three populations of microencapsulated antigens. Shahin teaches that oral administration of the FHA microcapsules

likely didn't work due to the fact that 100Ug was given and it is known in the art that less than 1% of an oral dose of DL-PLG microparticles successfully reach the Peyer's patches. It is noted that the Jones references teaches using 6mg of microparticles in its oral administration methods. One of ordinary skill in the art would know to increase the amount of microparticles and use similar amounts when administering a second or more population of microcapsules containing an antigen to the method taught by Jones et al. due to the knowledge available in the art. The prior art is replete with references documenting the successful induction of mucosal immune responses following oral administration of DL-PLG microspheres of several microencapsulated antigens (see Shanin et al page 1199, first full paragraph).

It is noted that the present specification provides no results from a method comprising orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation. Applicants argument against unpredictablity is invalid without results from their own experiments.

8. Claims 28-31, 33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt and Singh et al (Vaccine, 1998, 16(4): 346-352) and Shahin as set forth above and further in view of O'Hagan et al (US 5,603,960).

The combined teachings of Jones, Singh, Shahin and Eckhardt are set forth above. Both references, as stated above, teach that a protective Th2 (humoral/antibody) type response was seen. However, they do not particularly exemplify that the microcapsules are nanoparticles wherein at least 50% are less than 600nm.

As stated above, Singh et al disclose that diphtheria toxoid was encapsulated in microparticles prepared from polylactide-co-glycolide (PLG) polymers using a solvent evaporation technique (abstract). It is disclosed that rats were immunized with PLG microparticles containing the diphtheria toxoid with all microparticles being less than 10um. Another group of mice were given microparticles of greater than 10um. See page 348, column 1. It is disclosed that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 2).

O'Hagan et al describe methods for producing microparticles useful in the formulation of pharmaceutical compositions. Methods of immunizing mammals against diseases comprising administering to the mammal an effective amount of antigen-containing microparticles. Vaccines comprising a pharmaceutical composition comprising said microparticles are also disclosed. It is disclosed that the preferred average microparticle size is between 200 nm and 200um (column 3, lines 33-34). It is disclosed that when the microparticles are to be orally administered, the preferred size of the microparticles is preferably between 100 nanometers to 10 um in size (column 7, lines 21-23). It is preferred that the microparticles be administered orally (column 3, lines 40-41). It is disclosed that the microparticles are preferably made with a

biodegradable polymer (column 4, lines 63-3). The solvent media used in the solvent evaporation method to produce the microparticles is dependent upon the material to be encapsulated (column 4, lines 60-63). The preferred polymer for encapsulating the bioactive material is a polylactide polymer, or particularly a polylactide-co-glycolide polymer (column 5, lines 24-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use nanoparticles less than 600nm as taught by O'Hagan and Singh, or microparticles less than 5um as taught by Jones, because the prior art specifically discloses that particle uptake by M cells in the mouse gut is restricted to materials with diameters less than or equal to 10um (page 492, column 2) and that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1). O'Hagan teaches vaccine compositions comprising microparticles of 100nm to 10 um in size which are made of the same polymers as those used in the methods of Shanin and Jones and uses similar methods to produce the microparticles. Singh et al specifically discloses that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 2). Since Jones, also teach DL-PLG encapsulated antigen as vaccines, and specifically teach that the use of smaller microparticles allows for a more rapid phagocytosis and distribution, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the particles less than 500 or 600nm, absent unexpected or

unobvious results, because a person of ordinary skill in the art would expect such a microparticle to improve the immune response of the method. One of ordinary skill in the art would have a wide knowledge of the appropriate size to make the microparticles depending on their objectives given the large amount of literature available in the prior art at the time the invention was made.

9. Claims 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt, Shahin and Singh as applied to claims 21-25 and 27 above, and further in view of Andrianov (US Patent No. 5,807,757).

The teachings of Jones and Sing and Eckhardt are set forth above. However, they do not particularly teach that the microparticles were formed by coacervation.

Andrianov et al disclose a method for preparing polyphosphazene microspheres by coacervation (abstract). Andrianov et al disclose that the process of coacervation allows for the microspheres to be produced with a controlled microsphere size distribution without the use of elevated temperatures, organic solvents, water-insoluble core materials or complex manufacturing equipment, such as spray equipment and eliminates generation of the aerosol (column 2, lines 15-23 and lines 51-55). It is taught that the coacervation process is highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). It is specifically taught that this important for the preparation of microspheres for vaccine delivery since the uptakes of these microspheres by M

cells is limited to the particles having a diameter of 10um or less (column 2, lines 61-65). It is disclosed that biological material can be encapsulated by mixing the material with either polyphosphazene solution before microsphere preparation, or with prepared polyphosphazene microspheres (col. 2, lines 24-29). Andrianov et al teach that the phosphazene polyelectrolyte is preferably *biodegradable* to prevent eventual deposition and accumulation of polymer molecules at distant sites in the body, such as the spleen (column 4, lines 32-40). The paragraph bridging columns 5 and 6, disclose that the microspheres formed by coacervation, may be employed as carriers of a biological material such as an antigen, which is capable of eliciting an immune response in an animal. The antigen may be derived from a cell, bacterium, virus particle or a portion thereof and may be a protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, or combination thereof which elicits an immune response in an animal, including mammals, birds and fish (column 6,lines 1-10). It is taught that the microspheres which contain antigen may be administered as a vaccine by any method known to those skilled in the art that elicits an immune response, including parenterally, orally or by transmembrane or transmucosal administration (column 6, lines 30-40). The use of pharmaceutically acceptable carrier with the microspheres, i.e., PBS, is taught. It is taught that coacervation enables one to recover an increased yield of microspheres having a size in the micron range (up to 90 differential percent by volume and 95 differential percent by number), and produce microspheres of other sizes if needed without the use of elaborate equipment (column 5, lines 55-61). Example 9 teaches that 90% of particles by number and size are smaller than 6.6um, Example 6 teaches that

microparticles with a mean size between 4-6um were formed and Example 2 teaches that the percentage of microspheres under 10um is 90%(by volume) and 99.7% (by number).

It would have been prima facie obvious to one of ordinary skill in the art to produce the microparticles taught by the combination of Jones, Eckhardt, Shahin and Singh by the coacervation methods taught by Andrianov et al because the primary references teach that PLG are biodegradable polymers with a long history of safe use in humans and Andrianov specifically teach that coacervation methods have many advantages over solvent evaporation methods, such as highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). Absent evidence to the contrary, one of ordinary skill in the art would expect another biodegradable polymer, such as PLG, to work equally as well in the coacervation methods taught by Andrianov et al. and would allow for the production of a safe and effective microparticle vaccine.

10. Claims 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt, Shahin, Singh et al and O'Hagan et al (US 5,603,960) as applied to claims 28-31, 33 and 35-37 above, and further in view of Andrianov.

The combination of primary references do not particularly teach that the microparticles were formed by coacervation.

Andrianov et al disclose a method for preparing polyphosphazene microspheres by coacervation (abstract). Andrianov et al disclose that the process of coacervation allows for the microspheres to be produced with a controlled microsphere size distribution without the use of elevated temperatures, organic solvents, water-insoluble core materials or complex manufacturing equipment, such as spray equipment and eliminates generation of the aerosol (column 2, lines 15-23 and lines 51-55). It is taught that the coacervation process is highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). It is specifically taught that this important for the preparation of microspheres for vaccine delivery since the uptakes of these microspheres by M cells is limited to the particles having a diameter of 10um or less (column 2, lines 61-65). It is disclosed that biological material can be encapsulated by mixing the material with either polyphosphazene solution before microsphere preparation, or with prepared polyphosphazene microspheres (col. 2, lines 24-29). Andrianov et al teach that the phosphazene polyelectrolyte is preferably *biodegradable* to prevent eventual deposition and accumulation of polymer molecules at distant sites in the body, such as the spleen (column 4, lines 32-40). The paragraph bridging columns 5 and 6, disclose that the microspheres formed by coacervation, may be employed as carriers of a biological material such as an antigen, which is capable of eliciting an immune response in an animal. The antigen may be derived from a cell, bacterium, virus particle or a

portion thereof and may be a protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, or combination thereof which elicits an immune response in an animal, including mammals, birds and fish (column 6,lines 1-10). It is taught that the microspheres which contain antigen may be administered as a vaccine by any method known to those skilled in the art that elicits an immune response, including parenterally, orally or by transmembrane or transmucosal administration (column 6, lines 30-40). The use of pharmaceutically acceptable carrier with the microspheres, i.e., PBS, is taught. It is taught that coacervation enables one to recover an increased yield of microspheres having a size in the micron range (up to 90 differential percent by volume and 95 differential percent by number), and produce microspheres of other sizes if needed without the use of elaborate equipment (column 5, lines 55-61). Example 9 teaches that 90% of particles by number and size are smaller than 6.6um, Example 6 teaches that microparticles with a mean size between 4-6um were formed and Example 2 teaches that the percentage of microspheres under 10um is 90%(by volume) and 99.7% (by number).

It would have been prima facie obvious to one of ordinary skill in the art to produce the microparticles taught the primary references by the coacervation methods taught by Andrianov et al because the primary references teach that PLG are biodegradable polymers with a long history of safe use in humans and Andrianov specifically teach that coacervation methods have many advantages over solvent evaporation methods, such as highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation

microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). Absent evidence to the contrary, one of ordinary skill in the art would expect another biodegradable polymer, such as PLG, to work equally as well in the coacervation methods taught by Andrianov et al. and would allow for the production of a safe and effective microparticle vaccine.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

J Graser 9/10/03

Jennifer Graser
Primary Examiner
Art Unit 1645